

**REMARKS****Claim Rejection under 35 USC § 112**

Claims 1-4 are rejected under 35 USC § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner asserts that Claims 1-4 are indefinite because the variables represented by the R groups do not list all possible substituents which are included in the terms "substituted or unsubstituted".

As discussed in the Reply mailed to the United States Patent Office on February 28, 2006, the terms "substituted" and "unsubstituted" are commonly used terms of art, and are clear as written. It appears that the Examiner is objecting to the breadth of the claims rather than the clarity or definiteness of the claims. The breadth of the claims is not properly rejected under 35 USC § 112 second paragraph unless the Applicant has indicated that he intended the invention to be of a different scope than that defined in the claims (MPEP 2173.04):

Breadth of a claims is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169, USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear and if the applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Since Applicant has not indicated that he intended the invention to be of a different scope than that defined in the claims, and the scope of the subject matter is clear, the rejection is not proper and withdrawal of the rejection is respectfully requested.

Further, the Applicant would like to point the Examiner to the composition claims of US Patent 6,969,728 which is under obligation of assignment to the same Assignee as the instant application (and the entire contents of which are incorporated by reference in the instant Application (page 13 lines 22 – 24). The composition claims which issued in US Patent 6,969,728 (a copy of which was enclosed the Reply mailed to the United States Patent Office on February 28, 2006) are directed to compounds represented by Formula (I) as in the instant method claims. Many of the R groups of the composition claims which issued in this patent are similar in scope to the claims of the instant Application. This would indicate that the United

States Patent Office found these composition claims to be enabled and to comply with the written description requirement of 35 USC § 112 first paragraph.

Provisional Claim Rejection under the judicially created doctrine of Double Patenting

In the Office Action of October 31, 2005, the Examiner provisionally rejected Claims 1-26 under the judicially created of double patenting over Claims 1-20 of co-pending Application No. 10/719,701. The Examiner has maintained this rejection

As discussed in the Reply mailed to the United States Patent Office on February 28, 2006, the rejection is a provisional rejection because the claims of co-pending Application No. 10/719,701 have not been patented. Applicants will address the provisional double patenting rejection of Claims 1-26 in the subject application if the corresponding claims of co-pending U.S. Patent Application No. 10/719,701 are allowed or patented before the claims of the subject application.

If this provisional rejection is the only rejection remaining in either the subject application or co-pending Application No. 10/719,701 after entry and consideration of any Amendments, Applicants request that the Examiner withdraw the rejection and permit either the subject application or co-pending Application No. 10/719,701 to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)(1)).

Claim Rejection under 35 USC § 102 (a)

Claims 1-26 are rejected under 35 USC § 102(a) as being anticipated by Sneddon *et al.*, WO 01/87849.

In making this rejection the Examiner states that Sneddon *et al.*, teach a method of inhibiting tissue transplant as graft versus host disease (GVHD) and refers to page 14 line 30 of Sneddon *et al.*.

Applicant respectfully disagrees, the instant Claims are not anticipated by Sneddon *et al.*, for at least the following reasons.

Sneddon *et al.* teach treating GVHD. The instant Claim 1 is directed to a method for inhibiting tissue transplant rejection in a subject.

According to The American Heritage Stedman's Medical Dictionary. Houghton Mifflin Company, 2002. *Answers.com* 17 Feb. 2006. <http://www.answers.com/topic/graft-versus-host-disease> (a copy of which was enclosed the Reply mailed to the United States Patent Office on February 28, 2006) graft versus host disease is defined as:

A type of incompatibility reaction of transplanted cells against host tissues that possess an antigen not possessed by the donor. Also called *graft versus host reaction*.

Thus, graft versus host disease is when transplanted cells reject the host's tissue; not when the host rejects a transplanted tissue. Therefore, GVHD is the reverse reaction of a transplant rejection where the host cell attacks the transplanted tissue. The Indiana Blood and Marrow Transplantation states in <http://www.ibmtindy.com/faq/graft.htm> a copy of which is attached as **Exhibit A** (emphasis added) that:

Patients who receive a stem cell transplant from an identical twin donor, are infused with stem cells that are truly identical to their own. All other recipients of donor stem cells, whether from HL:A-identical sibling donors, or from matched unrelated donors, will be infused with stem cells that are different from the patient's own stem cells. The human immune system is based on recognition of "self" against "different or "foreign". Immune systems are trained to attack and destroy "foreign" proteins, whether they are bacteria, viruses, cancer cells, or transplanted tissues. Thus, the differences between the tissues of the patient and the stem cells of the donor lead to a fight and attempts of one to destroy the other. The patient's tissues (host tissues) will try to destroy the stem cells. This process is called "rejection" and is more frequent as the donor and recipient are less well matched. Rejection of the stem cells results in failure of the new stem cells to grow and produce sufficient blood cells. The patient continues to have low white cell and platelet counts and continues to be at risk of infection and bleeding. Repeating the transplant is the only way of helping the patient. Often the re-transplant does not succeed in raising the white cells fast enough to prevent fatal infections. Fortunately, rejection is uncommon, since the issues of the patient have been suppressed by the chemotherapy and radiation given to destroy the malignant cells ("preparative regimen").

*A "reversed rejection" can also occur. Under this scenario, the healthy donor stem cells recognize the patient's tissues as foreign and attack them. This is the "transplant against the patient", or "Graft-versus-Host" reaction. The complications is called "Graft-versus-Host Disease" (GvHD).*

GVHD occurs typically in bone marrow transplants where the host is immunocompromised following radiation therapy. Therefore, in these cases the transplant rejection by the host is unlikely as the host is immunocompromised.

Furthermore, GVHD occurs typically in bone marrow cell transplants rather than tissue transplants. The instant claims are directed to methods for treating tissue transplant rejections.

Sneddon *et al.*, teach treating GVHD; they do not teach inhibiting a tissue transplant rejection. Therefore the instant claims are novel in light of Sneddon *et al.*

Further, Claims 2, 4-8 and 12-15 are novel and non-obvious for yet another reason. Specifically, these claims are directed to a method of inhibiting a chronic tissue transplant rejection in a subject comprising administering to the subject an effective amount of a compound represented by Formula (I). Chronic transplant rejection is a specific type of transplant rejection the underlying causes of which are not fully understood. Moreover, chronic transplant rejection may occur in patients who are being successfully treated for acute transplant rejection. The instant specification page 1 line 23 to page 2 line 5 states:

Whereas acute rejection is suppressed with immunosuppressive protocols, treatment for chronic rejection is less well defined. Acute rejection and chronic rejection have significantly different characteristics as immune responses. For example, chronic rejection occurs over time, typically several months to years after engraftment, even in the presence of successful immunosuppression. It involves multiple factors and processes of the host and is usually the result of a prolonged process of wound healing the host undergoes post-transplant. Therefore, chronic rejection is not totally immunological in origin and additional cause(s) are not fully understood. They may include ischemic insult, denervation of the transplanted tissue, hyperlipidemia and hypertension associated with immunosuppressive drugs.

The above facts would indicate that it would not be obvious to one of skill in the art that one compound could be used to treat both acute and chronic transplant rejections, rather they would indicate that the opposite were true, that is, that different compounds would be required to treat the two different diseases.

Furthermore, there are currently no known treatments for chronic transplant rejection. The instant specification page 2 lines 19 - 20 states:

The chronic rejection process is not inhibited by any known therapeutic regimen at this time.

Further, [http://en.wikipedia.org/wiki/Transplant\\_rejection](http://en.wikipedia.org/wiki/Transplant_rejection) a copy of which is attached as **Exhibit B** states (emphasis added):

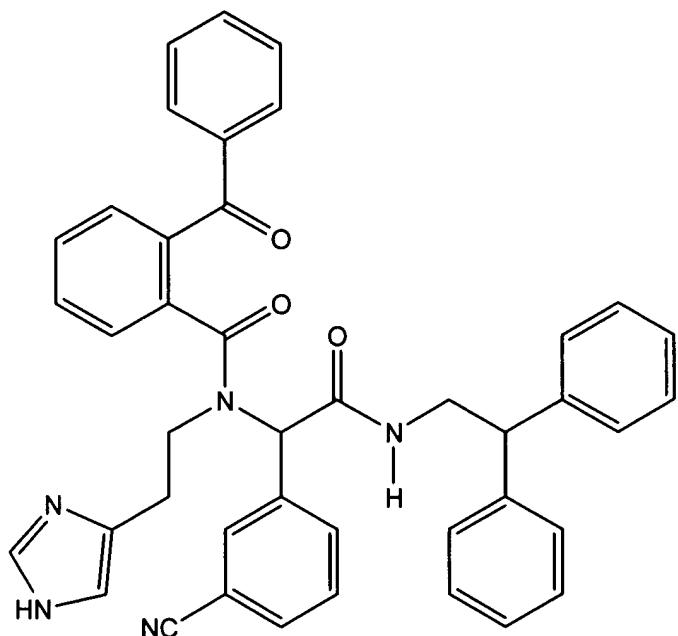
***Chronic rejection is irreversible and cannot be treated effectively.*** The only definitive treatment is re-transplantation, if necessary.

The UK National Kidney Foundation also states in <http://www.kidney.org.uk/Medical-Info/transplant/txrej.html>, a copy of which is attached as **Exhibit C** (emphasis added):

***There is no treatment for chronic rejection that can be guaranteed to be successful,*** but some patients get an improvement if the anti-rejection drugs are changed.

The Applicant has now discovered that the compounds described in the instant specification are effective in preventing chronic transplant rejection. The instant specification page 2 lines 27 to page 3 line 12 states:

In one example, the histopathological evidence of chronic rejection was inhibited in two mouse models by Compound 1, shown below. In the first model, chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at eight weeks post surgery was inhibited by treatment with 75 mg/kg/day of



## Compound 1

Compound 1 alone during the two weeks following surgery. In the second model, chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at 120 days post surgery was inhibited when treatment with 75 mg/kg/day of Compound 1 during the two weeks following surgery was combined with a single administration of 250  $\mu$ g of anti-CD154 monoclonal antibody immediately following transplant surgery. Treatment with anti-CD154 monoclonal antibody alone suppresses acute rejection, but is ineffective in preventing chronic rejection of transplanted tissue.

In summation, while Sneddon *et al.*, teach treating GVHD, they do not teach treating chronic transplant rejection. As discussed above, chronic transplant rejection is a specific type of transplant rejection, the underlying causes of which are not fully understood and for which there is currently no known treatment. The Applicant has discovered that the compounds described in the instant specification are effective in preventing chronic transplant rejection. Specifically, Applicant has found that the instant compounds inhibit chronic rejection of fully MHC class II mismatched transplanted hearts in recipient mice at eight weeks post surgery. Therefore, the instant invention represents a surprising and unexpected improvement in methods for inhibiting rejection of tissue transplants.

Sneddon *et al.*, not only do not provide a teaching of treating a tissue transplant rejection, they further do not provide a specific teaching of treating a chronic transplant rejection. Therefore the claims are novel and patentable in light of Sneddon *et al.*, and withdrawal of the rejection is respectfully requested.

**CONCLUSION**

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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